



02 JUN 2005

(43) International Publication Date  
17 June 2004 (17.06.2004)

PCT

(10) International Publication Number  
WO 2004/050620 A3(51) International Patent Classification<sup>7</sup>: C07D 213/40, 209/20, 209/16, C07K 5/06, 5/08, C07C 259/06, 235/04, A61K 31/16, 31/405, 31/44

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(21) International Application Number:  
PCT/CA2003/001893

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(22) International Filing Date: 3 December 2003 (03.12.2003)

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(25) Filing Language: English

(84) Designated States (regional): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(26) Publication Language: English

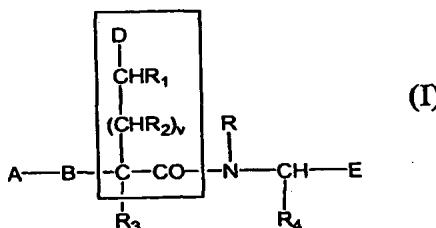
## Published:

(30) Priority Data:  
60/430,382 3 December 2002 (03.12.2002) US

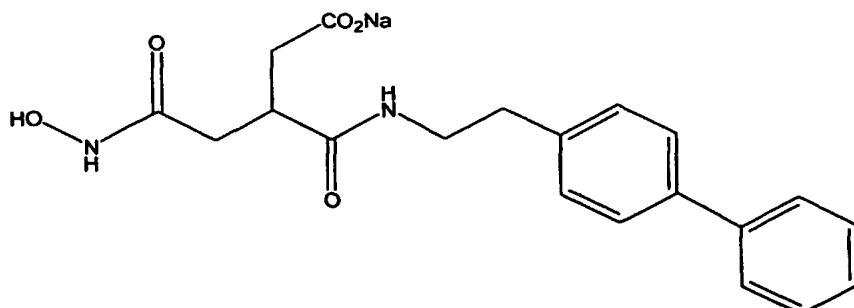
— with international search report  
 — before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

[Continued on next page]

(54) Title: DERIVATIVES OF SUCCINIC AND GLUTARIC ACIDS AND ANALOGS THEREOF USEFUL AS INHIBITORS OF PHEX



(57) Abstract: The present invention relates to derivatives of succinic and glutaric acids and analogues thereof, having the following general formula (I), useful as inhibitors of PHEX. These derivatives are useful for promoting generation of bone mass and treating or preventing diseases or conditions associated with a phosphate metabolism defect. Methods for preparation and intermediates are also disclosed.



WO 2004/050620 A3



**(88) Date of publication of the international search report:**  
19 August 2004

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/CA 03/01893

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7	C07D213/40	C07D209/20	C07D209/16	C07K5/06	C07K5/08
	C07C259/06	C07C235/04	A61K31/16	A61K31/405	A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07K C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, EMBASE, BIOSIS, PAJ, WPI Data

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Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	WO 03/084997 A (BAUDRY JEROME ;YOKUM SCOTT (US); ANDREWS ROBERT (US); BANNER WILLI) 16 October 2003 (2003-10-16) page 199; example 49 ---	1, 4
X	WO 99/11606 A (LILJEBRIS CHARLOTTA ;BARF TJEERD (SE); SCHOSTAREZ HEINRICH JOSEF () 11 March 1999 (1999-03-11) example 21 ---	1, 4
X	WO 97/05865 A (BRENNER MITCH ;FIBROGEN INC (US); HO WEN BIN (US)) 20 February 1997 (1997-02-20) examples 20,22 ---	1, 4
X	EP 0 412 595 A (MERCK & CO INC) 13 February 1991 (1991-02-13) examples 5,19,30 ---	1, 4
	-/-	

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
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- \*O\* document referring to an oral disclosure, use, exhibition or other means
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\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the International search

Date of mailing of the International search report

1 June 2004

14/06/2004

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## INTERNATIONAL SEARCH REPORT

International Application No  
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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SERVAL, V. ET AL: "In vitro and in vivo inhibition of N-acetyl-L-aspartyl-L-glutamate catabolism by N-acylated L-glutamate analogs" retrieved from STN Database accession no. 117:43302 XP002280633 RN 142255-59-2 & JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS (1992), 260(3), 1093-100 , ---	1
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## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/CA 03/01893

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; OVENS, ANNABEL ET AL: "Design and synthesis of acidic dipeptide hydroxamate inhibitors of procollagen C-proteinase" retrieved from STN Database accession no. 134:1980 XP002280636 RNs 309122-09-0, 308122-10-3 &amp; JOURNAL OF PEPTIDE SCIENCE (2000), 6(9), 489-495 ,</p> <p>---</p>	1,4
X	<p>DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; RINNOVA, MARKETA ET AL: "An expedient method for the solid-phase synthesis of <math>\alpha</math>-aminoalkyl phosphonopeptides" retrieved from STN Database accession no. 137:201580 XP002280637 RNs 453540-07-3, 453540-15-3 &amp; TETRAHEDRON LETTERS (2002), 43(22), 4103-4106 ,</p> <p>---</p>	1
Y	<p>EP 0 254 032 A (SCHERING CORP) 27 January 1988 (1988-01-27) abstract; examples 15-17</p> <p>---</p>	1-4, 10-14
Y	<p>EP 0 566 157 A (SCHERING CORP) 20 October 1993 (1993-10-20) abstract; claims</p> <p>---</p>	1-4, 10-14
Y	<p>ROWE P S N: "THE ROLE OF THE PHEX GENE (PEX) IN FAMILIES WITH X-LINKED HYPOPHOSPHATAEMIC RICKETS" CURRENT OPINION IN NEPHROLOGY AND HYPERTENSION, RAPID SCIENCE, LONDON, GB, vol. 7, no. 4, 1998, pages 367-376, XP001002174 ISSN: 1062-4813 page 369; figure 2</p> <p>---</p> <p>-/-</p>	1-4, 10-14

## INTERNATIONAL SEARCH REPORT

International Application No

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BOILEAU GUY ET AL: "Characterization of PHEX endopeptidase catalytic activity: Identification of parathyroid-hormone-related peptide107-139 as a substrate and osteocalcin, PPI and phosphate as inhibitors" BIOCHEMICAL JOURNAL, THE BIOCHEMICAL SOCIETY, LONDON, GB, vol. 355, no. 3, 1 May 2001 (2001-05-01), pages 707-713, XP002204778 ISSN: 0264-6021 page 712, column 2 ---	1-4, 10-14
Y	MIMURA, TETSUTARO ET AL: "A novel class of enkephalinase inhibitors containing a C-terminal sulfo group" JOURNAL OF MEDICINAL CHEMISTRY ( 1992 ), 35(3), 602 -8 , XP002280631 table II ---	1-4, 10-14
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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/CA 03/01893

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
**Although claims 5–9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.**
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
**see FURTHER INFORMATION sheet PCT/ISA/210**
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple Inventions in this International application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claim 1 relates to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. Formula (I) is practically only made of variants (A, B, D, E, R, etc) which are defined by unspecific expressions like "zinc ligand", "zinc ligand bearing moiety", "substituted alkyl", "lower alkyl", "substituted lower alkyl", "lower alkoxy", "cycloalkyl", "aryl", "substituted aryl", "heteroaryl", "amino acid", "symmetrical disulfide", etc. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, taking into account the compounds prepared in the examples and closely related homologous compounds, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds wherein A represents one of the groups listed and E is H, CONHCH<sub>3</sub>, COOH, COOAlk, CONH<sub>2</sub>, CONHCH(COOH)CH<sub>2</sub>OH, CH<sub>2</sub>CH<sub>2</sub>OH, CH<sub>2</sub>OH, CH<sub>2</sub>COOH. The cases wherein R<sub>1</sub>+R<sub>2</sub>, R<sub>1</sub>+R<sub>3</sub>, R+R<sub>4</sub>, R<sub>11</sub>+R<sub>1</sub> and R<sub>11</sub>+R<sub>2</sub> may form a ring have not been searched.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No  
PCT/CA 03/01893

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International application No

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